Lung replacement therapies for acute respiratory failure

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ABSTRACT

Acute respiratory failure is one of the critical conditions with an increased mortality. In order to reverse lung injury and reduce the mortality rate, several lung replacement therapies have been developed, including the extracorporeal membrane oxygenation, the intravascular oxygenator and carbon dioxide removal device, the intravenous membrane oxygenator and the thoracic artificial lung. This article aims to present the properties, indications and advantages of these devices.

Key words: artificial organs, extracorporeal membrane oxygenation, respiratory insufficiency

INTRODUCTION

Acute respiratory failure is one of the critical conditions that endangers patients' lives and hence is associated with an increased mortality. In recent years, people have been endeavoring to explore new approaches for the effective treatment of this critical condition in the hope of reversing lung injury and reducing mortality. (1) Currently, several lung replacement therapies are in use, including the extracorporeal membrane oxygenation (ECMO), the intravascular oxygenator and carbon dioxide (CO2) removal device (IVOX), the intravenous membrane oxygenator (IMO) and the thoracic artificial lung (TAL). The oxygenator is the central component of the cardiopulmonary bypass (CPB) or ECMO circuit. The oxygenators provide gas exchange by contact between blood and the gas phase, either with hollow fibers or a folded silicone membrane. (2) An oxygen-rich gas mixture is passed through the oxygenator in an opposite direction to blood flow, promoting oxygen diffusion into the blood. (3) This article will briefly present the clinical application of the devices as well as patients' outcomes.

ECMO

ECMO is a mechanical support system used to aid heart and lung function in patients with severe respiratory or cardiac failure aiming at promoting oxygenation and later also at carbon dioxide removal. The technology is similar to CPB, as used during cardiac surgery, but modified for prolonged use at the bedside in the intensive care unit. The differences between ECMO and CPB are shown in table 1.

Since 1885, when Frey and Gruber developed the first extracorporeal blood oxygenation device, until early 1970's when Hill et al. successfully treated a patient with prolonged extracorporeal oxygenation (Bramson membrane lung) for acute post-traumatic respiratory failure (shock-lung syndrome), oxygenators have undergone sustained technical modifications, which brought about the emergence of the membrane oxygenator and surface-heparinized extracorporeal circulation technique. (4)

ECMO currently is divided into two types: venoarterial (VA) and venovenous (VV). VA ECMO, support blood circulation by improving cardiac output, while VV ECMO is a type of extracorporeal CO2 removal system (ECCO2R). (5) In 1978, Gattinoni et al. (6) reported their results of mechanical pulmonary ventilation with low-frequency positive pressure ventilation and extracorporeal CO2 removal (LFPPV-ECCO2R) in five lambs, where cannulations were performed via the subclavian artery-external jugular vein, and blood was pumped through an extracorporeal carbon dioxide membrane lung (CDML), with a surface area of 1.6 m2. The CO2 elimination function with this device seemed to be good. Subsequently, they reported their clinical application of LFPPV-ECCO2R in 19 acute respiratory distress syndrome (ARDS) patients with an overall mortality rate of 23%. (7) Recent studies showed that reduction in tidal volumes to 4 mL/kg and concomitant use of ECCO2R were more effective for permissive hypercapnia in ARDS patients. (8)

Table 1. The differences between ECMO and cardiopulmonary bypass.

Variable	ECMO	Cardiopulmonary bypass
Access	Cervical cannulation	Transthoracic cannulation
Anesthesia	Local anesthesia	General anesthesia
Support time	3-10 days	Hours
Purpose	Intrinsic recovery of the lungs and heart	Support during various types of cardiac surgical procedures
Place of use	Bedside intensive care unit	Operating theater

ECMO, extracorporeal membrane oxygenation.

Since 1986 extracorporeal circuits and membrane lungs coated with Carmeda Bioactive Surface (CBAS) for extracorporeal lung assistance (ECLA) have been used in 14 patients suffering from ARDS. The patients were on ECLA for 3-55 days with a survival rate of 43%. However, the major drawback of this device was bleeding due to systemic heparinization. (9)

Conrad et al. (10) reported their experience in the treatment of acute hypercapnic respiratory failure or hypoxemic respiratory failure managed with permissive hypercapnia with pumpless extracorporeal arteriovenous carbon dioxide removal (AVCO2R), which was deployed via femoro-femoral cannulations with heparin administered 100-200 mg/kg and an activated coagulation time (ACT) of 200-250 s. Decrease of PaCO2 for 1-2 h of support and reduction of minute ventilation for the first 32 h of support were significant while patients' hemodynamics were stable.

Later on, this technique was widely used in the support of respiratory failure. Hong et al. (11) succeeded in rescuing a neonate with complex congenital heart defects presenting with life-threatening hypoxemia and heart arrest. Hammainen et al. (12) examined the early outcome in patients with end-stage pulmonary disease who were bridged to lung transplantation with the aid of ECMO. Mean ECMO support of 17 days (range, 1-59 days) in 13 patients obtained a success for bridging in 81% of cases and 1-year survival in 75%. Almond et al. (13) reported, among 773 children (median age, 6 months) with ECMO support >14 days, that 45% of them were successfully bridged to transplantation, and the overall survival was 47%. Chauhan et al. (14) reported on 94 patients who received ECMO support following cardiac surgery for repair of transposition of the great arteries (TGA), with an intact ventricular septum, who showed a survival rate to discharge of 64.8%. Indications for ECMO after pediatric cardiac surgery have been increasing, although survival rates after ECMO support following cardiac surgery are 75% for infants and 52% for adults. (15) Merrill et al. (16) reported, for children with cardiac dysfunction, that survivors had a shorter duration of ECMO support than non-survivors. The infant oxygenator, tested in sheep, showed an adequate oxygenation capacity, a CO2 removal capacity, and a small alteration in hemoglobin and

platelets without a significant decrease in leucocytes. (17) The limitations of ECMO include the requirement for a large and complex blood pump and oxygenator system, the necessity for a surgical procedure for cannulation, the need for systemic anticoagulation, labor intensive implementation, the exceedingly high cost, and a high rate of complications, including bleeding and infection, protein absorption, and platelet adhesion on the surface of the oxygenator membrane. As a result of these limitations, ECMO has become limited for neonatal respiratory failure.

IVOX

Intravenous oxygenation represents a potential respiratory support modality for patients with acute respiratory failure or with acute respiratory exacerbations. The first IVOX, capable of removing 30% of CO2, was invented by Mortensen and Berry in the late 1980's. (18) The IVOX is surgically deployed into the inferior or superior vena cava via a femoral or jugular venotomy, by which gas exchange occurs through the hollow fibers driven by a vacuum pump. (19) There is no extracorporeal circulation of blood. Gas exchange is accomplished as the patient's blood flows through the hollow fibers via inlet and outlet gas conduits for oxygen infusion and CO2 elimination. (20) Clinical experience confirms the safety and simplicity of IVOX, but the mean gas-transfer values represent only 25% of basal requirements. (21) Like ECMO, the IVOX system has numerous limitations including a moderate rate of achievable gas exchange, difficulty in device implantation, a relatively high rate of adverse events, and device malfunctions, such as blood-to-gas leaks due to broken hollow fibers. (22) In order to overcome these shortcomings, IVOX has been improved in terms of: 1) materials for synthesis of the hollow fibers, as in the superior properties of synthesized fluorinated aromatic polyimide in comparison to polypropylene, silicone-coated polypropylene and polydimethylsiloxane; (23) 2) number and arrangements of the hollow fibers with reference to the superior oxygenation capacity of the net to the linear and braided arrangements; (24) and 3) an increase of gas exchange of the hollow fibers by arranging the matted hollow fiber membranes around a centrally positioned tripartite balloon. (25) Besides thrombotic complications, circulatory obstruction and

barotrauma might occur with the use of IVOX. (19)

IMO

The current IMO device uses a constrained fiber bundle made by wrapping hollow fiber fabric around a concentrically located polyurethane balloon. The constrained fiber bundle is intentionally smaller than vessel lumen size, which allows for shunt flow of blood past the device to reduce flow resistance. (26) Like IVOX, IMO consists of a bundle of manifolded hollow fibers, and is intended for intravenous placement within the superior and inferior vena cava. (27) An IMO with a design goal of 50% of basal oxygen and CO2 exchange requirements has been successfully used for treatment of end-stage ARDS. However, it was considered that IVOX and IMO are surface-limited and may provide inadequate gas exchange. (28)

TAL

TALs are an alternative device for bridging patients with respiratory failure to lung transplantation. TALs are attached to the pulmonary circulation, and thus their blood flow is provided by the right ventricle. Current TALs possess blood flow impedances greater than the natural lungs, resulting in low cardiac output when implanted in series with the natural lung or in parallel under exercise conditions. (29)

A compliant TAL has been developed for acute respiratory failure or as a bridge to transplantation. The device uses microporous, hollow fiber bundles. The bundle is placed within thermoformed polyethylene terephthalate glucose modified housing with a gross volume of 800 cm3. The development goal was to increase TAL compliance, lower TAL impedance, and improve right ventricular function during use. Prototypes were tested in vitro and in vivo in eight pigs between 67 and 79 kg to determine hemodynamic and gas transfer properties. Device resistance was 1.9 and 1.8 mmHg/L/min at a flow rate of 4 L/min in vitro and in vivo, respectively. Approximately 75% of the resistance was at the inlet and outlet. The in vivo TAL oxygen and CO2 transfer rates were 188 and 186 mL/min, respectively. The new design has a markedly improved compliance and

excellent gas transfer but also possesses inlet and outlet resistances that have to be reduced in future designs. (30) These devices were implanted in Yorkshire pigs via a median sternotomy with an end-to-side anastomosis to the pulmonary artery and left atrium. These experiments suggest that such an artificial lung can temporarily support the gas transfer requirements of adult humans without overloading the right ventricle. (31) Sato et al. (32) tested a TAL (MC3 Biolung) in 10 sheep. The total oxygen transfer was stable, and TAL blood outlet oxygen saturations did not change significantly with time, averaging 99.5% ± 1.5% during the experimental period. The device was redesigned to improve hemodynamics and right ventricular function. Eash et al. (33) evaluated the plasma resistant hollow fiber membranes used in TALs in terms of gas permeance and plasma resistance, which impose the great-est constraint upon artificial lung design for sufficient gas exchange. Zhu et al. (34) proved that phosphorylcholine played an important role in maintaining blood compatibility when it was used in synthesized materials.

CONCLUSIONS

ECMO and IVOX have largely benefited patients with respiratory insufficiency. Due to the disparities of indications and configurations of the two devices, the utilizing perspectives are different. The complexity, risk potential and cost of ECMO significantly prohibit its wide use in clinical practice. IVOX is a novel therapeutic approach for respiratory failure. It is a good choice in hospitals that cannot establish ECMO for critical patients. IVOX does not need an additional bypass circuit, thereby protecting blood components, reducing energy loss and decreasing the infective opportunity. IVOX is free of blood priming, maintenance becomes simple, and the costs are significantly decreased. Pump-free TAL is now in the process of manufacture. An ideal implantable artificial lung should be flexible, with good gas exchange function and good biological compatibility. Modifications on structure and physical and chemical stability of the medical membranes, arrangements of hollow fibers and prevention of membranous pollution are being undertaken to enhance the properties of the artificial devices. Further research should be concentrated on the improvement of its properties including gas exchange, blood compatibility, hemodynamic compatibility and configuration of the device.

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